Drug treatment of chronic venous insufficiency and venous ulceration: a review

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Summary

Treatment of venous insufficiency and venous ulceration has for many years relied on established principles of compression and limb elevation. Drug treatment has been of little benefit. In recent years, a better understanding of the pathological mechanisms underlying skin damage in venous disease has allowed more rational pharmacotherapeutic approaches to be made. This review examines these, with special reference to current theories of the cause of venous ulceration.

Introduction

Venous ulcers affect a total of approximately 100 000 patients in the UK at any one time, indicating a prevalence of between 0.1 and 0.2% of the population[1,2]. In addition there is a larger number of patients at risk of developing leg ulceration, either by virtue of a past history of an ulcer or because of the presence of liposclerotic skin changes. A number of studies in this country, Czechoslovakia and the USA have estimated that 1% of the adult population are affected by venous ulceration at some time in their lives[3,4,5].

The condition clearly has great socio-economic significance in addition to its medical aspect; it has been estimated to cost the National Health Service more than £100 000 000 per annum in dressings, district nurse provision and inpatient care[6]. Nevertheless, treatment for this common and distressing condition has not advanced signficantly over the past century, being based now, as in 1891, on the principles of compression and elevation.

This is clearly an unsatisfactory and ineffective therapy for many patients, as the number of chronic, unhealed ulcers testifies. In general drug treatment has been unsatisfactory; as a consequence, a number of exotic and unlikely compounds have been in vogue at various times this century, usually very transiently. Over the past 20 years, however, improvements in our understanding of the pathophysiological mechanisms at work in the disease have pointed the way towards rational pharmacotherapy.

Antibiotics

'Virtually every antibiotic that has ever been produced has been used to treat venous ulcers but there is very little evidence that they help healing unless the ulcer is contaminated by a single pathogenic organism'[7]. This quotation from Browse *et al.* summarizes the present position regarding systemic antibiotic treatment in venous ulceration. Naturally, clinical infection of an ulcer must be treated, but this is best done by local ulcer toilet, unless cellulitis or septicaemia supervene. The possible exception to this rule is the use of metronidazole. There is some evidence that this compound given orally increased the rate of healing of both venous and pressure ulcers when they are infected with *Clostridium* and other anaerobes[8]. Even then, however, systemic treatment may not be superior to topical application; Jones *et al.* have demonstrated the rapid effectiveness of metronidazole soaked dressings in such cases[9]. In general, systemic antibiotics do not play a role in the management of the uncomplicated venous ulcer.

Zinc

Ensuring an adequate diet is essential for any healing process. It is self-evident that the tendency of a venous ulcer to heal will be impaired if the general nutritional status of the patient is poor. For a number of years, special attention was given to the concept that, in particular, zinc levels were depressed in patients with venous ulcers and that supplementation might speed healing. Greaves and Skillen, in a widely quoted paper, reported complete healing in 13 of 18 patients with previously intractable ulceration after a 4 month course of 220 mg zinc sulphate three times daily[10]. During this period they continued with their previous conservative treatment as outpatients. Pretreatment serum zinc levels were found to be significantly lower in the patient group than in controls.

A subsequent Swedish study[11] indicated that the benefit conferred by supplementary zinc was only apparent when serum zinc was low to start with; in their study of 27 patients with chronic ulcers, this applied in 14 cases. In the other 13 with normal zinc levels, ulcer healing was no quicker with zinc than with placebo; indeed, the placebo group appeared to do better.

In a later report, Greaves and Ive published their results over a longer period, in a double-blind trial of oral zinc in 38 patients with venous ulcers[12]. They were unable to confirm their initial good results, with only three of the treated group and two of the placebo group showing complete healing after 4 months. Serum zinc levels were not measured in this study. These negative results were confirmed by Myers and Cherry[13] in a study of 40 ulcer patients and by Phillips *et al.*[14] in 42 patients; in both studies, healing occurred at the same rate in zinc-treated and control patients.

Recently, Schraibmann and Stratton have compared the nutritional status of venous ulcer patients with that of age- and sex-matched controls[15]. Of 11 indices thought to represent nutritional deficiency, only one (haemoglobin) was significantly lower in patients with

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venous ulcers. Serum zinc was, in fact, slightly higher on average in this group than in controls. It would seem, therefore, that zinc supplements to the diet are unlikely to be of much benefit to the majority of patients, although they may have a role in the management of those few patients with severe nutritional problems.

Diuretics

Generalized leg oedema is a feature of proximal large vein obstruction, while localized oedema is commonly associated with patches of lipodermatosclerosis (LDS)[7]. Simple diuretics are not generally used in oedema due to venous disease, since the increased permeability to proteins seen in venous hypertension leads to a protein rich oedema which is unsuitable for such treatment[16]. In addition, haemoconcentration may occur, leading to reduced capillary blood flow and the risk of deep venous thrombosis.

Oedema reduction *per se* is probably not an important consideration in the treatment of venous ulcers. Myers *et al.* have shown that healing of ulcers is unrelated to the amount of leg swelling; in their words: 'the edema and the ulcer are due to the same cause, probably venous stasis, and any therapy which does not improve venous drainage is probably doomed to failure'[17]. Although the concept of venous stasis is now thought to be unsound, the second half of their statement is likely to remain true.

Hydroxyrutosides

Hydroxyrutosides are a class of flavanoid drug derived from plant glycosides. They initially gained favour 20 years ago when experimental studies indicated that they reduced capillary permeability following burns in dogs. A number of clinical studies evaluating their effect on a variety of symptoms associated with CVI followed[18,19]. In general these indicated that hydroxyrutosides appeared to be marginally more effective than placebo in reducing aching, tiredness, muscle cramps and other symptoms which one might imagine are difficult to evaluate objectively. The drugs do appear to be more effective than placebo in reducing oedema[20]; the clinical relevance of this is uncertain. One study of venous ulcer healing seemed to show an increased incidence of healed ulcers after 2 weeks of treatment with hydroxyrutosides compared with placebo, but this difference disappeared after 4 weeks of treatment[21]. A study on the effect of rutosides on symptoms in 112 patients with venous insufficiency included four with ulceration. All four took rutosides for 8 weeks; only one showed any evidence of improvement[22].

In the past 2 years there has been a revival of interest in rutosides, especially in Europe. It has been demonstrated that they reduce capillary filtration rate in patients with CVI[23]; their effect on oedema reduction has also been confirmed[24]. A recent symposium at the International Union of Angiology on the use of hydroxyrutosides in venous disease contained a number of reports on their symptomatic value[25-27], but no evidence of a beneficial effect on venous ulcers.

There is now good evidence that rutosides are helpful in alleviating symptoms in patients with venous insufficiency; however, they have no role to play in the healing of venous ulceration.

Fibrinolytic therapy

The concept of an oxygen diffusion barrier causing skin hypoxia has been central to our understanding of the pathogenesis of skin damage in venous disease ever since the theory was first proposed by Browse and Burnand in 1982[28]. The model they put forward involved the increased extravasation of fibrinogen as a result of venous hypertension; this fibrinogen then polymerizes into an insoluble pericapillary fibrin cuff which, it is suggested, impairs the passage of oxygen and other nutrients from blood vessel to skin. In addition, the same workers demonstrated convincingly that fibrinolytic activity was markedly reduced in patients with venous disease[29-31].

This theory led to attempts to reverse the damaging cutaneous effects of venous hypertension by enhancing fibrinolysis.

Initial impressions were encouraging. The St Thomas' group evaluated the effect of stanozolol, an anabolic steroid with profibrinolytic properties, on 14 patients with longstanding LDS, without active ulceration[32]. After 3 months, all showed clinical improvement both subjectively and objectively (by mapping the area of LDS). Serum parameters of fibrinolytic activity improved in all cases. One might criticize the study for including three patients in whom the LDS was not associated with any venous abnormality. However, this pilot study justified a larger trial of fibrinolytic treatment in CVI.

This was performed as a 6-month double-blind crossover trial on 23 patients with longstanding LDS which had not responded to compression hosiery[33]. All patients continued with stockings during the trial. The area of liposclerotic skin fell during treatment with both stanozolol and placebo. The rate at which it fell was faster on stanozolol than on placebo, although this difference did not reach statistical significance. Leg volume as measured by plethysmography increased on the steroid, presumably as a result of fluid retention. Skin biopsy analysis suggested but did not prove that tissue fibrin was reduced by stanozolol treatment; foot vein pressure reduction on exercise was improved to the same extent on both active and placebo treatment. All but one patient described subjective improvement during the trial but were unable to differentiate between the active and placebo periods. The exception to this was in pain relief which was significantly better while taking the steroid.

Overall, the results seem to have been unspectacular, indicating a possible small benefit from fibrinolytic treatment rather than a major advance in therapy. This impression was confirmed in a further double-blind cross-over study of 60 patients performed in our unit (McMullin *et al.*, unpublished data). Stanozolol+stockings caused a reduction of liposclerotic skin area of 28% over 6 months. However, when the separate contributions of the two treatment elements were calculated using multivariate analysis of variance, the effect attributable to stanozolol alone was not statistically significant.

One of the problems in evaluating the response of LDS to treatment is the paucity of hard end-points that can be measured; how does one quantify, for example, lightening of pigmentation, or reduction of induration? Treatment of venous ulceration, by contrast, allows the simple question to be asked: healed or not healed? Fibrinolytic treatment for venous ulceration has been evaluated in one trial

of 75 patients[34]. Patients were allocated to receive either stanozolol or placebo for up to 420 days, with conventional compression treatment in all cases. In an interim report, the authors found complete healing in 26 of 40 ulcers in the stanozolol group and 27 of 44 in the placebo group, indicating no benefit from active over placebo treatment.

In summary, one may say that fibrinolytic enhancement may be of minor benefit in the symptomatic treatment of LDS, but that it does not appear to improve ulcer healing. Before dismissing the concept, one must note that only one agent, stanozolol, has been extensively studied for this purpose, and it is possible that more potent fibrinolytic agents could be more effective.

Recent advances

Disappointment with fibrinolytic treatment, together with some theoretical objections to the notion of impaired oxygen diffusion in LDS[35,36], has led to the search for alternative lines of pharmacological attack on venous skin damage. It has been suggested that white blood cells may adhere more readily to capillary endothelium when venous pressure is raised, and that this may lead to inappropriate white cell activation with subsequent release of proteolytic enzymes and toxic free radicals[37]. Two agents which modify white cell activation have recently been evaluated in patients with venous ulceration with promising results.

Prostaglandin E_1 (PGE_1) has a number of profound effects on the microcirculation, including reduction of white cell activation, platelet aggregation inhibition, small vessel vasodilatation and reduction of vessel wall cholesterol levels[38]. It has been evaluated in the treatment of various aspects of arterial disease; less work has been done on its use in venous ulceration. An early trial of the use of intravenous PGE_1 in ulcers of both arterial and venous aetiology reported improvement in four out of five venous ulcers on PGE_1 as opposed to four out of seven on placebo - hardly a dramatic result[39]. A recent trial has yielded rather more impressive findings[40]. Forty-four patients with proven venous ulceration took part in a double-blind placebo-controlled trial. Each received an infusion of PGE_1 (or placebo) over 3 h daily for 6 weeks, in addition to standard dressings and compression bandaging. Those on PGE_1 showed a significant improvement in such parameters as oedema reduction, symptoms and 'ulcer core', based on depth, diameter etc. Perhaps more importantly, 8 of 20 patients on active treatment healed their ulcers completely within the trial period, whereas only 2 of 22 controls did so.

The reason for the different outcomes in these two trials probably relates to the dose of PGE_1 given. In Beitner *et al.*'s study, only two infusions were given. These consisted of 360 μg of PGE_1 in 3 litres of isotonic saline over 72 h, a month apart. In the second trial, 60 μg were given over 3 h every day for 6 weeks - a total dose 3.5 times bigger than that in the earlier study. Although this rather intensive way of treating ulcers is not, at first sight, attractive, the cost of such treatment must be weighed against the many millions of pounds spent each year in this country on the outpatient care of unhealed ulcers.

A perhaps more practical form of effective oral treatment has recently been reported. Pentoxifylline has been used for the treatment of claudication for a number of years, with moderate success[41]. It was thought that it may act by improving red cell deformability and thus improve oxygen delivery to ischaemic tissue. Recent work on the drug indicates that it actually has a potent effect on inhibition of cytokine-mediated neutrophil activation[42]. The same workers also showed it to reduce white cell adhesion to endothelium and to reduce the release of superoxide free radicals produced in the so-called respiratory burst characteristic of neutrophil degranulation. Theoretically, therefore, it should be of benefit in venous disease if the white cell activation model described above is valid.

Weitgasser evaluated the effect of the drug in a double blind placebo-controlled trial of 59 patients with venous ulcers[43]. Of 30 patients on active treatment, 26 'improved'; this was assessed by comparing photographs of the ulcer before and after treatment. Only 13 of 29 patients on placebo improved, a statistically significant difference. Unfortunately no firm data are given regarding the numbers of healed and unhealed ulcers at the end of the trial, which rather dilutes its impact. Herger subsequently studied the effect of the drug on 73 patients with ulceration, in 42 of whom the cause was venous insufficiency[44]. The protocol of drug administration was rather vague; the dosages 'in most cases' were 400 mg three or four times a day, and some patients also received pentoxifylline infusions. Treatment lasted for 8 weeks. Sixty-two of the 73 ulcers healed; we do not know how many of the specifically venous ulcers are included in this figure. The trial was not placebo-controlled.

A Greek study examined the effect of 1200 mg pentoxifylline per day on 10 patients with proven venous ulcers, with partial or complete healing in eight after 6 weeks[45]. Unfortunately this trial did not use a control group. A rather more rigorous trial has recently been reported by Colgan *et al.*[46]. This was a multicentre placebo-controlled double-blind prospective study of 80 patients with venous ulcers. After 6 months of treatment with 1200 mg/day of pentoxifylline or placebo, 23 of 38 patients in the active arm had a healed ulcer, while 12 of 42 in the placebo-treated arm had the same result. This difference was statistically significant. (In both trials, patients continued with conventional hosiery and general ulcer care.) The success of this agent lends further weight to the concept that white cell trapping and activation are important in the pathogenesis of LDS and venous ulceration.

Future developments

The development of effective drug treatment for the skin damage caused by venous disease will depend upon an improved understanding of the pathophysiology - a subject of lively controversy in phlebological circles at the moment. Iloprost, a synthetic prostacyclin analogue, has been used with success in the treatment of arterial and diabetic ulcers[47]. The mechanism of action of prostacyclin includes increased fibrinolytic activity[48]; the drug also has profound effects on leucocyte activity by reducing aggregation and adherence to endothelium[49,50] in addition to its better known effects on platelet behaviour[51]. It would therefore seem to be an agent well worth evaluating in venous disease, as its modes of action are of potential benefit in both the fibrin cuff and white cell trapping models of venous skin damage. Following an encouraging pilot study (unpublished data), a

multi-centre trial of the agent in venous ulceration is now under way.

Two other agents of potential interest are Buflomedil and Gingko biloba. Buflomedil has been used to alleviate the symptoms of peripheral vascular disease[52]; it reduces blood viscosity in diabetics[53]; it acts as a vasodilator[54] and improves TcPo2 in peripheral ischaemia[55]. If small vessel perfusion is impaired in venous disease, such an agent may have therapeutic value. Gingko biloba is a plant-derived flavanoid which has been shown to reduce free radical generation from activated leucocytes[56] and also to act as a free radical scavenger[57]. It ameliorates reperfusion injury in a rat intestine model[58] and reduces neutrophil chemotaxis mediated by platelet-activating factor[59]. If white cell activation is an important element in venous skin damage, this compound might be expected to show beneficial effects.

Conclusion

The main methods of treating chronic venous insufficiency continue to be physical: elevation of the limb, compression hosiery, cleaning, dressing and (occasionally) skin grafting of ulcers, with surgical correction of superficial or perforating vein incompetence where appropriate. In the absence of any very effective agents, drug treatment until recently has been of minor importance. Diuretics and antibiotics do not have significant roles in the management of the condition. Hydroxyrutosides and fibrinolytic agents seem to be of some benefit in improving symptoms of venous insufficiency, but have been disappointing in the treatment of ulceration. Recent reports of improved ulcer healing with drugs acting on the microcirculation (prostaglandin E_1, pentoxifylline) are encouraging, but more trials are necessary before they can be said to have become part of the standard armamentarium in the treatment of venous disease.

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